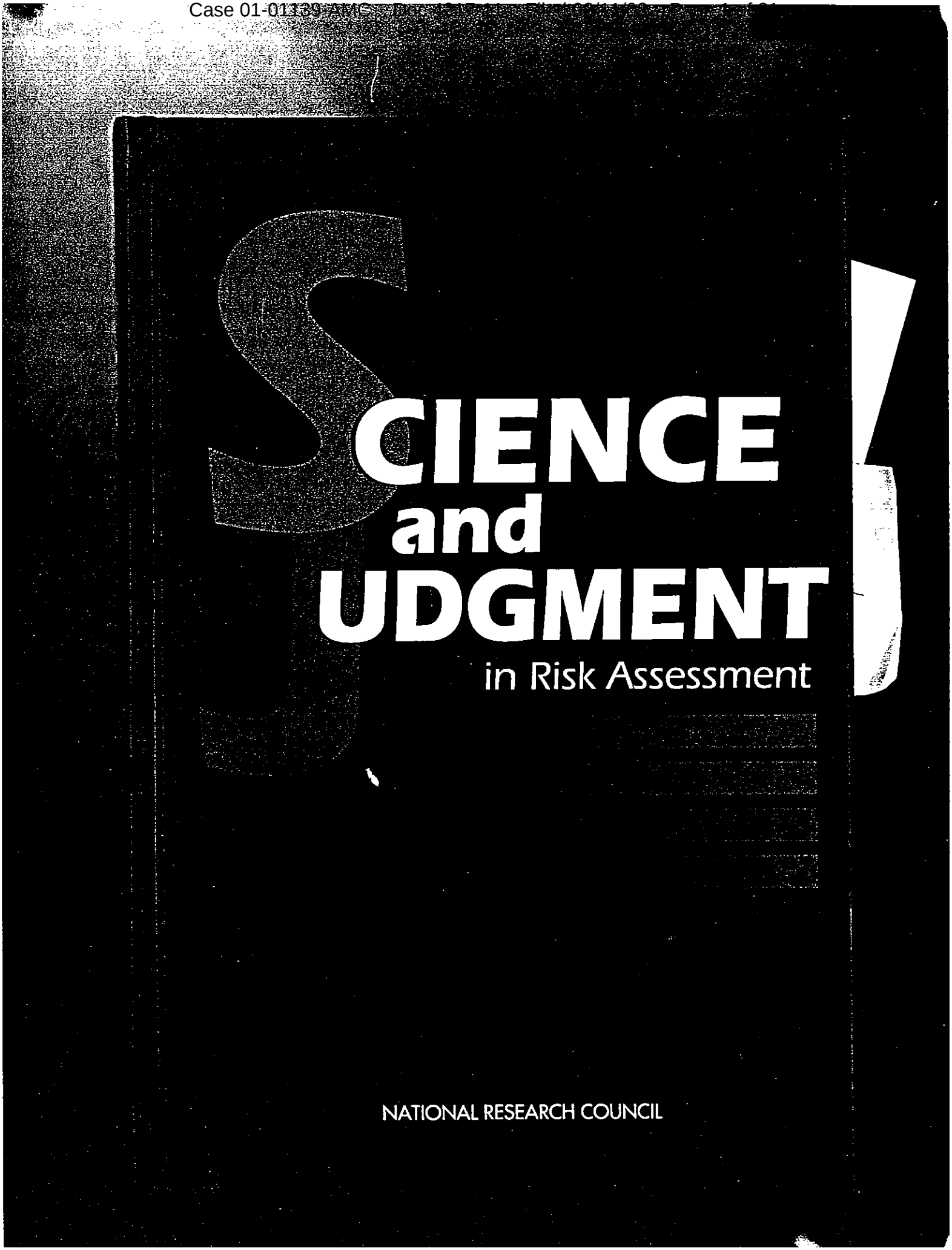
SCIENCE
and
UDGMENT
in Risk Assessment
NATIONAL RESEARCH COUNCIL

SCIENCE and JUDGMENT in Risk Assessment

Committee on Risk Assessment of Hazardous Air Pollutants

Board on Environmental Studies and Toxicology

Commission on Life Sciences

National Research Council

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This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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Preface

In the Clean Air Act Amendments of 1990, Congress directed the administrator of the Environmental Protection Agency (EPA) to engage the National Academy of Sciences (NAS) in a review of the methods that EPA uses to estimates toxicological risk. The resulting charge to the National Research Council (NRC) can be summarized in a short set of questions:

1. Given that quantitative risk assessment is essential for EPA's implementation of the Clean Air Act, is EPA conducting risk assessments in the best possible manner?
2. Has EPA developed mechanisms for keeping its risk-assessment procedures current in the face of new developments in science?
3. Are adequate risk-related data being collected to permit EPA to carry out its mandates?
4. What, if anything, should be done to improve EPA's development and use of risk assessments?

To meet the congressional mandate, and in response to the request from the administrator of EPA, the National Research Council established the Committee on Risk Assessment of Hazardous Air Pollutants under the the Board on Environmental Studies and Toxicology. The committee consisted of 25 members with expertise in medicine, epidemiology, chemistry, chemical engineering, environmental health, law, pharmacology and toxicology, risk assessment, risk management, occupational health, statistics, air monitoring, and public health. It included academics, industry scientists, public advocates, and state and local public-health officials.

The first meeting of the committee was held on October 31, 1991. In the first several meetings, presentations were made to the committee by committee members and by individuals or representatives of groups with special concerns in the development and use of risk assessment. Among the latter were presenters on behalf of the American Industrial Health Council, the Chemical Manufacturers Association, the American Petroleum Institute, the American Iron and Steel Institute, the American Chemical Society, such official public-health groups as the Texas Air Control Board and the State and Territorial Air Pollution Program Administrators, and such public-interest groups as the Natural Resources Defense Council and the Environmental Defense Fund. Presentations were also made by the representative of a paint manufacturer and by a senior member of an environmental consulting company. The committee also was greatly aided by the previous reports and workshops of the NRC's Committee on Risk Assessment Methodology.

Early in the course of its deliberations the committee developed a set of issues for consideration and reply by EPA's Office of Air and Radiation and its Office of Research and Development. EPA's responses were presented to the committee during the committee's meetings in late March 1992.

James Powell, of the U.S. Senate staff, described to the committee both the legislative history of the Clean Air Act Amendments and the concerns of senators in the evolution of EPA's development of regulations. Greg Wetstone, of the U.S. House of Representatives staff, spoke to the committee about the need for accurate risk assessments and exposure measures. Henry Habicht, Michael Shapiro, Robert Kellum, and William Farland of EPA discussed where EPA was in risk assessment and how it got there. Their briefings enabled the committee to get off to a quick start in its work.

The committee was substantially helped in its activities by strong support from the NRC and BEST staff: Richard D. Thomas, the program director; Deborah D. Stine, the study director; Marvin A. Schneiderman, senior staff scientist; Norman Grossblatt, editor; Anne M. Sprague, information specialist; Ruth E. Crossgrove, information specialist; Ruth P. Danoff, project assistant; and Shelley A. Nurse and Catherine M. Kubik, senior project assistants.

Finally, we must express our thanks and appreciation to the hard-working members of the committee, who struggled through long meetings, read mountains of documents, listened with interest and concern to many presentations, and then prepared what we consider to be a thoughtful, comprehensive, and balanced report.

Kurt Isselbacher, M.D.
Chairman

Arthur Upton, M.D.
Vice Chairman

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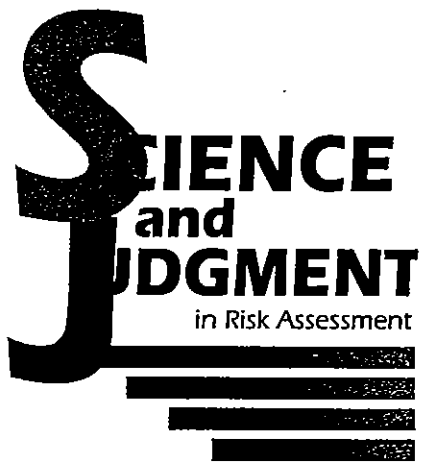

Executive Summary

In recent decades, the public has become increasingly aware of seemingly innumerable reports of health threats from the environment. Myriad announcements about pesticides in food, pollutants in the air, chemical contaminants in drinking water, and hazardous-waste sites have created public concern about the chemical products and byproducts of modern industrial society. Alongside that concern is public skepticism about the reliability of scientific predictions concerning possible threats to human health. The skepticism has arisen in part because scientists disagree. But it is also apparent that many people want to understand the methods for assessing how much their exposures to chemicals threaten their health and well-being.

Many environmental issues that have risen to public prominence involve carcinogens—substances that can contribute to the development of cancer. Sometimes the decision that a substance is a carcinogen is based on evidence from workers exposed to high concentrations in the workplace, but more often it is based on evidence obtained in animals exposed to high concentrations in the laboratory. When such substances are found to occur in the general environment (even in much lower concentrations), efforts are made to determine the exposed population's risk of developing cancer, so that rational decisions can be made about the need for reducing exposure. However, scientists do not have and will not soon have reliable ways to measure carcinogenic risks to humans when exposures are small. In the absence of an ability to measure risk directly, they can offer only indirect and somewhat uncertain estimates.

Responses to these threats, often reflected in legislation and regulations, have led to reduced exposures to many pollutants. In recent years, however,

concerns have arisen that the threats posed by some regulated substances might have been overstated and, conversely, that some unregulated substances might pose greater threats than originally believed. Questions have also been raised about the economic costs of controlling or eliminating emissions of chemicals that might pose extremely small risks. Debates about reducing risks and controlling costs have been fed by the lack of universal agreement among scientists about which methods are best for assessing risk to humans.

Epidemiological studies—typically, comparisons of disease rates between exposed and unexposed populations—are not sufficiently precise to find that a substance poses a carcinogenic risk to humans except when the risk is very high or involves an unusual form of cancer. For this reason, animal studies generally provide the best means of assessing potential risks to humans. However, laboratory animals are usually exposed to toxicants at concentrations much higher than those experienced by humans in the general population. It is not usually known how similar the toxic responses in the test animals are to those in humans, and scientists do not have indisputable ways to measure or predict cancer risks associated with small exposures, such as those typically experienced by most people in the general environment.

Some hypotheses about carcinogens are qualitative. For example, biological data might suggest that any exposure to a carcinogen poses some health risk. Although some scientists disagree with that view or believe that it is not applicable to every carcinogen, its adoption provides at least a provisional answer to a vexing scientific question, namely whether people exposed to low concentrations of substances that are known to be carcinogenic at high concentrations are at *some* risk of cancer associated with the exposure. The view has dominated policy-making since the 1950s but is not always consistent with new scientific knowledge on the biological mechanisms of chemically induced cancer.

Beginning in the 1960s, toxicologists developed quantitative methods to estimate the risks associated with small exposures to carcinogens. If it were reliable, quantitative risk assessment could improve the ability of decision-makers and to some extent the public to discriminate between important and trivial threats and improve their ability to set priorities, evaluate tradeoffs among pollutants, and allocate public resources accordingly. In short, it could improve regulatory decisions that affect public health and the nation's economy.

During the 1970s and 1980s, methods of risk assessment continued to evolve, as did the underlying science. It became increasingly apparent that the process of carcinogenesis was complex, involving multiple steps and pathways. The concept that all cancer-causing chemicals act through mechanisms similar to those operative for radiation was challenged. Some chemicals were shown to alter DNA directly and hence to mimic radiation. But evidence developed that other chemicals cause cancer without directly altering or damaging DNA, for example, through hormonal pathways, by serving as mitogenic stimuli, or by causing excess cell death with compensatory cell proliferation. Biologically

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based and pharmacokinetic models were introduced in some cases to describe exposure-response relationships more accurately. During the same period, substantial advances were made in modeling the dispersion of airborne materials from sources to receptors and in conducting exposure assessments. Furthermore, important advances have been made in the last 10 years in understanding the basic biology of chemical toxicity. All these advances are beginning to have a major impact on the estimation of risks associated with hazardous air pollutants.

REGULATION OF HAZARDOUS AIR POLLUTANTS

Before the enactment of the Clean Air Act Amendments of 1990 (1990 Amendments), Section 112 of the Clean Air Act required that the Environmental Protection Agency (EPA) set emission standards for hazardous air pollutants "to protect the public health with an ample margin of safety." In 1987, the District of Columbia Circuit Court of Appeals, in *Natural Resources Defense Council v. EPA* (824 F.2d 1146) interpreted this language to mean that EPA must first determine the emissions level that is safe—one that represents an acceptable degree of risk—and then add a margin of safety in light of the uncertainties in scientific knowledge about the pollutant in question. The agency was permitted to consider technological feasibility in the second step but not in the first.

In response, EPA decided that it would base its regulatory decisions largely on quantitative risk assessment. The agency adopted a general policy that a lifetime cancer risk of one in 10,000 for the most exposed person might constitute acceptable risk and that the margin of safety should reduce the risk for the greatest possible number of persons to an individual lifetime risk no higher than one in 1 million (10^{-6}).

The 1990 Amendments rewrote Section 112 to place risk assessment in a key role but one secondary to technology-based regulation. As altered, Section 112 defines a list of substances as hazardous air pollutants, subject to addition or deletion by EPA. Sources that emit hazardous air pollutants will be regulated in two stages. In the first, technology-based emissions limits will be imposed. Each major source of hazardous air pollutants must meet an emission standard, to be issued by EPA, based on using the maximum achievable control technology (MACT). Smaller sources, known as area sources, must meet emissions standards based on using generally available control technology.

In the second stage, EPA must set "residual-risk standards that protect public health with an ample margin of safety if it concludes that the technology-based standards have not done so." The establishment of a residual-risk standard is required if the MACT emission standard leaves a lifetime cancer risk for the most exposed person of greater than one in a million. In actually setting the standard, though, EPA is free to continue to use its present policy of accepting higher risks. Quantitative risk assessment techniques will be relevant to this second stage of regulation, as well as to various decisions required in the first stage.

CHARGE TO THE STUDY COMMITTEE

Section 112(o) of the Act (quoted in full in Appendix M) directs the EPA to arrange for the National Academy of Sciences to:

- Review the methods used by EPA to determine the carcinogenic risk associated with exposure to hazardous air pollutants from sources subject to Section 112;
- Include in its review evaluations of the methods used for estimating the carcinogenic potency of hazardous air pollutants and for estimating human exposures to these air pollutants;
- Evaluate, to the extent practicable, risk-assessment methods for noncancer health effects for which safe thresholds might not exist.

The Academy's report must be considered by EPA in revising its present risk assessment guidelines.

CURRENT RISK-ASSESSMENT PRACTICES

Methods for estimating risk to humans exposed to toxicants have evolved steadily over the last few decades. Not until 1983, however, was the process codified in a formal way. In that year, the National Research Council released *Risk Assessment in the Federal Government: Managing the Process.* This publication, now known also as the Red Book, provided many of the definitions used throughout the environmental-health risk-assessment community today. The Red Book served as the basis for the general description of risk assessment used by the present committee.

Risk assessment entails the evaluation of information on the hazardous properties of substances, on the extent of human exposure to them, and on the characterization of the resulting risk. Risk assessment is not a single, fixed method of analysis. Rather, it is a systematic approach to organizing and analyzing scientific knowledge and information for potentially hazardous activities or for substances that might pose risks under specified conditions.

In brief, according to the Red Book, risk assessment can be divided into four steps: hazard identification, dose-response assessment, exposure assessment, and risk characterization.

- *Hazard identification* involves the determination of whether exposure to an agent can cause an increased incidence of an adverse health effect, such as cancer or birth defects, and characterization of the nature and strength of the evidence of causation.
- *Dose-response assessment* is the characterization of the relationship between exposure or dose and the incidence and severity of the adverse health effect. It includes consideration of factors that influence dose-response relationships, such as intensity and pattern of exposure and age and lifestyle variables

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- *Exposure assessment* is the determination of the intensity, frequency, and duration of actual or hypothetical exposures of humans to the agent in question. In general, concentrations of the substance can be estimated at various points from its source through the environment. An important component of exposure assessment is emission characterization, i.e., determination of the magnitude and properties of the emissions that result in exposures. This is usually accomplished by measuring and analyzing emissions, but that is not always possible. Therefore, modeling is often used instead to establish the relationship between emissions and environmental concentrations of the substance. Inputs to such a model should include data on residence and activities of the exposed population.
- *Risk characterization* combines the assessments of exposure and response under various exposure conditions to estimate the probability of specific harm to an exposed individual or population. To the extent feasible, this characterization should include the distribution of risk in the population. When the distribution of risk is known, it is possible to estimate the risk to individuals who are most exposed to the substance in question.

Closely related to risk assessment is risk management, the process by which the results of risk assessment are integrated with other information—such as political, social, economic, and engineering considerations—to arrive at decisions about the need and methods for risk reduction. The authors of the Red Book advocated a clear conceptual distinction between risk assessment and risk management, noting, for instance, that maintaining the distinction between the two would help to prevent the tailoring of risk assessments to the political feasibility of regulating the substance in question. But they also recognized that the choice of risk-assessment techniques could not be isolated from society's risk-management goals. The result should be a process that supports the risk-management decisions required by the Clean Air Act and that provides appropriate incentives for further research to reduce important uncertainties on the extent of health risks.

In 1986, EPA issued risk-assessment guidelines that were generally consistent with the Red Book recommendations. The guidelines deal with assessing risks of carcinogenicity, mutagenicity, developmental toxicity, and effects of chemical mixtures. They include default options, which are essentially policy judgments of how to accommodate uncertainties. They include various assumptions that are needed for assessing exposure and risk, such as scaling factors to be used for converting test responses in rodents to estimated responses in humans.

As risk-assessment methods have evolved and been applied with increasing frequency in federal and state regulation of hazardous substances, regulated industries, environmental organizations, and academicians have leveled a broad

array of criticisms regarding the processes used by EPA. The concerns have included

- The lack of scientific data quantitatively relating chemical exposure to health risks.
- The divergence of opinion within the scientific community on the merits of the underlying scientific evidence.
- The lack of conformity among reported research results needed for risk characterization—e.g., the use of different methods for describing laboratory findings, which makes it difficult to compare the data from different laboratories and apply them in risk characterizations.
- The uncertainty of results produced by theoretical modeling, which is used in the absence of measurements.
- In response to its mandates, EPA has traditionally adopted risk assessments that for the most part incorporate conservative default options (i.e., those that are more likely to overstate than to understate human risk).
- As scientific knowledge increases, the science policy choices made by the agency and Congress should have less impact on regulatory decision-making. Better data and increased understanding of biological mechanisms should enable risk assessments that are less dependent on conservative default assumptions and more accurate as predictions of human risk.

STRATEGIES FOR RISK ASSESSMENT

The committee observed that several common themes cut across the various stages of risk assessment and arise in criticisms of each individual step. These themes are as follows:

- *Default options.* Is there a set of clear and consistent principles for modifying and departing from default options?
- *Data needs.* Is enough information available to EPA to generate risk assessments that are protective of public health and are scientifically plausible?
- *Validation.* Has the EPA made a sufficient case that its methods and models for carrying out risk assessments are consistent with current scientific information available?
- *Uncertainty.* Has EPA taken sufficient account of the need to consider, describe, and make decisions in light of the inevitable uncertainty in risk assessment?
- *Variability.* Has EPA sufficiently considered the extensive variation among individuals in their exposures to toxic substances and in their susceptibilities to cancer and other health effects?
- *Aggregation.* Is EPA appropriately addressing the possibility of interactions among pollutants in their effects on human health, and addressing the consideration of multiple exposure pathways and multiple adverse health effects?

By addressing each of those themes in each step in the risk-assessment process, EPA can improve the accuracy, precision, comprehensibility, and utility of the entire risk-assessment process in regulatory decision making.

Flexibility and the Use of Default Options

EPA's risk-assessment guidelines contain a number of "default options." These options are used in the absence of convincing scientific knowledge on which of several competing models and theories is correct. The options are not rules that bind the agency; rather, they constitute guidelines from which the agency may depart when evaluating the risks posed by a specific substance. For the most part, the defaults are conservative (i.e., they represent a choice that, although scientifically plausible given existing uncertainty, is more likely to result in overestimating than underestimating human risk).

EPA has acted reasonably in electing to formulate guidelines. EPA should have principles for choosing default options and for judging when and how to depart from them. Without such principles, the purposes of the default options could be undercut. The committee has identified a number of criteria that it believes ought to be taken into account in formulating such principles: protecting the public health, ensuring scientific validity, minimizing serious errors in estimating risks, maximizing incentives for research, creating an orderly and predictable process, and fostering openness and trustworthiness. There might be additional relevant criteria.

The choice of such principles goes beyond science and inevitably involves policy choices on how to balance such criteria. After extensive discussion, the committee found that it could not reach consensus on what the principles should be or on whether it was appropriate for this committee to recommend principles. Thus, the committee decided not to do so. Appendix N contains papers by several committee members containing varied perspectives on the appropriate choice of principles. Appendix N-1 advocates the principle of "plausible conservatism" and N-2 advocates the principle of the maximum use of scientific information in selection of default options. These papers do not purport to represent the views of all committee members.

The committee did agree, though, that EPA often does not clearly articulate in its risk-assessment guidelines that a specific assumption is a default option and that EPA does not fully explain in its guidelines the basis for each default option. Moreover, EPA has not stated all the default options in the risk-assessment process or acknowledged where defaults do not exist.

EPA's practice appears to be to allow departure from a default option in a specific case when it ascertains that there is a consensus among knowledgeable scientists that the available scientific evidence justifies departure from the default option. The agency relies on its Scientific Advisory Board and other expert bodies to determine when such a consensus exists. But EPA has not articulated criteria for allowing departures.

Recommendations

- EPA should continue to regard the use of default options as a reasonable way to deal with uncertainty about underlying mechanisms in selecting methods and models for use in risk assessment.
- EPA should explicitly identify each use of a default option in risk assessments.
- EPA should clearly state the scientific and policy basis for each default option.
- The agency should consider attempting to give greater formality to its criteria for a departure from default options, in order to give greater guidance to the public and to lessen the possibility of ad hoc, undocumented departures from default options that would undercut the scientific credibility of the agency's risk assessments. At the same time, the agency should be aware of the undesirability of having its guidelines evolve into inflexible rules.
- EPA should continue to use the Science Advisory Board and other expert bodies. In particular, the agency should continue to make the greatest possible use of peer review, workshops, and other devices to ensure broad peer and scientific participation to guarantee that its risk-assessment decisions will have access to the best science available through a process that allows full public discussion and peer participation by the scientific community.

Validation: Methods and Models

Some methods and models used in emission characterization, exposure assessment, hazard identification, and dose-response assessment are specified as default options. Others are sometimes used as alternatives to the default options. The predictive accuracy and uncertainty of these methods and models for risk assessment are not always clearly understood or clearly explained.

A threshold model (i.e., one that assumes that exposures below some level will not cause health effects) is generally accepted for reproductive and developmental toxicants, but it is not known how accurately it predicts human risk. The fact that current evidence on some toxicants, most notably lead, does not clearly reveal a safe threshold has raised concern that the threshold model might reflect the limits of scientific knowledge, rather than the limits of safety.

EPA has worked with outside groups to design studies to refine emission estimates. However, it does not have guidelines for the use of emission estimates in risk assessment, nor does it adequately evaluate the uncertainty in the estimates.

EPA has relied on Gaussian-plume models to estimate the concentrations of hazardous pollutants to which people are exposed. These representations of airborne transport processes are approximations. EPA focuses primarily on stationary outdoor emission sources of hazardous air pollutants. It does not have a

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specific statutory mandate to consider all sources of hazardous air pollutants, but this should not deter the agency from assessing indoor sources to provide perspective in considering risks from outdoor sources.

EPA uses the Human-Exposure Model (HEM) to evaluate exposures from stationary sources. It estimates exposures and risk for both individuals and populations. For individuals, it has traditionally used a technique to determine what is called the maximally exposed individual (MEI) by estimating the highest exposure concentration that might be found among the broad distribution of possible exposures. Estimation of the maximum exposure is based on a variety of conservative assumptions, e.g., that the MEI lives directly downwind from the pollution source for his or her entire 70-year lifetime and remains outdoors the entire time. Traditionally, only exposure by inhalation is considered. Recently, in accordance with recommendations of the agency's Science Advisory Board, EPA has begun to replace the MEI estimate with two others: the high-end exposure estimate (HEEE) and the theoretical upper-bound exposure (TUBE).

In dose-response assessment, EPA has traditionally treated almost all chemical carcinogens as inducing cancer in a similar manner, mimicking radiation. It assumes that a linearized multistage model can be used to extrapolate from epidemiological observations (e.g., occupational studies) or experimental observations at high doses in laboratory animals down to the low doses usually experienced by humans in the general population.

Recommendations

- EPA should more rigorously establish the predictive accuracy and uncertainty of its methods and models and the quality of data used in risk assessment.
- EPA should develop guidelines for the amount and quality of emission information required for particular risk assessments and for estimating and reporting uncertainty in emission estimates, e.g., the predictive accuracy and uncertainty associated with each use of the HEM for exposure assessment.
- EPA should evaluate the Gaussian-plume models under realistic conditions of acceptable distances (based on population characteristics) to the site boundaries, complex terrain, poor plant dispersion characteristics, and the presence of other structures in the vicinity. Furthermore, EPA should consider incorporating such state-of-the-art techniques as stochastic-dispersion models.
- EPA should use a specific conservative mathematical technique to estimate the highest exposure likely to be encountered by an individual in the exposure group of interest.
- EPA should use bounding estimates for screening assessments to determine whether further levels of analysis are necessary. For further analyses, the committee supports EPA's development of distributions of exposures based on actual measurements, results from modeling, or both.
- EPA should continue to explore and, when scientifically appropriate, in-

corporate pharmacokinetic models of the link between exposure and biologically effective dose (i.e., dose reaching the target tissue).

- EPA should continue to use the linearized multistage model as a default option but should develop criteria for determining when information is sufficient to use an alternative extrapolation model.
- EPA should develop biologically based quantitative methods for assessing the incidence and likelihood of noncancer effects in human populations resulting from chemical exposure. These methods should incorporate information on mechanisms of action and differences in susceptibility among populations and individuals that could affect risk.
- EPA should continue to use as one of its risk-characterization metrics, upper-bound potency estimates of the probability of developing cancer due to lifetime exposure. Whenever possible, this metric should be supplemented with other descriptions of cancer potency that might more adequately reflect the uncertainty associated with the estimates.

Priority-Setting and Data Needs

EPA does not have the exposure and toxicity data needed to establish the health risks associated with all 189 chemicals identified as hazardous air pollutants in the 1990 Amendments. Furthermore, EPA has not defined how it will determine the types, quantities, and quality of data that are needed to assess the risks posed by facilities that emit any of those 189 chemicals or how it will determine when site-specific emission and exposure data are needed.

Recommendations

- EPA should compile an inventory of the chemical, toxicological, clinical, and epidemiological literature on each of the 189 chemicals identified in the 1990 Amendments.
- EPA should screen the 189 chemicals to establish priorities according to procedures described by the committee for assessing health risks, identify data gaps, and develop incentives to expedite the generation of data by other government agencies (e.g., the National Toxicology Program, the Agency for Toxic Substances and Disease Registry, and state agencies), industry, and academe.
- In addition to stationary sources of hazardous air pollutants, EPA should consider mobile and indoor sources; the latter might be even more important than outdoor sources. The agency should also explicitly consider all direct and indirect routes of exposure, such as ingestion and dermal absorption.
- EPA should develop a two-part scheme for classifying evidence on carcinogenicity that would incorporate both a simple classification and a narrative evaluation. At a minimum, both parts should include the strength (quality) of the evidence, the relevance of the animal model and results to humans, and the

relevance of the experimental exposures (route, dose, timing, and duration) to those likely to be encountered by humans.

Variability

Many types of variability enter into the risk-assessment process: variability within individuals, among individuals, and among populations. Types of variability include nature and intensity of exposure and susceptibility to toxic insult related to age, lifestyle, genetic background, sex, ethnicity, and other factors.

Interindividual variability is not generally considered in EPA's cancer risk assessments. The agency's consideration of variability has been limited largely to noncarcinogenic effects, such as asthmatic responses to sulfur dioxide exposure. Analyses of such variability usually form the basis of decisions about whether to protect both the general population and sensitive individuals.

Recommendations

- Federal agencies should sponsor molecular, epidemiological, and other types of research to examine the causes and extent of interindividual variability in susceptibility to cancer and the possible correlations between susceptibility and such covariates as age, race, ethnicity, and sex. Results should be used to refine estimates of risks to individuals and the general population.
- EPA should adopt a default assumption for differences in susceptibility among humans in estimating individual risks.
- EPA should increase its efforts to validate or improve the default assumption that humans on average have the same susceptibility as humans in epidemiological studies, the most sensitive animals tested, or both.
- EPA's guidelines should clearly state a default assumption of nonthreshold, low-dose linearity for genetic effects on which adequate data might exist (e.g., data on chromosomal aberrations or dominant or X-linked mutations) so that a reasonable quantitative estimate of genetic risk to the first and later generations can be made for environmental chemical exposure.
- The distinction between uncertainty and individual variability should be maintained rigorously in each component of risk assessment.
- EPA should assess risks to infants and children whenever it appears that their risks might be greater than those of adults.

Uncertainty

There are numerous gaps in scientific knowledge regarding hazardous air pollutants. Hence, there are many uncertainties in risk assessment. When the uncertainty concerns the magnitude of a quantity that can be measured or inferred from assumptions, such as exposure, the uncertainty can be quantified. Other uncertainties pertain to the models being used. These stem from a lack of

knowledge needed to determine which scientific theory is correct for a given chemical and population at risk and thus which assumptions should be used to derive estimates. Such uncertainties cannot be quantified on the basis of data.

The upperbound point estimate of risk typically computed by EPA does not convey the degree of uncertainty in the estimate. Thus, decision-makers do not know the extent of conservatism, if any, that is provided in the risk estimate.

Formal uncertainty analysis can help to inform EPA and the public about the extent of conservatism that is embedded in the default assumptions. Uncertainty analysis is especially useful in identifying where additional research is likely to resolve major uncertainties.

Uncertainty analysis should be an iterative process, moving from the identification of generic uncertainties to more refined analyses for chemical-specific or industrial plant-specific uncertainties. The additional resources needed to conduct the more specific analyses can be justified when the health or economic impacts of the regulatory decision are large and when further research is likely to change the decision.

Recommendations

- EPA should conduct formal uncertainty analyses, which can show where additional research might resolve major uncertainties and where it might not.
- EPA should consider in its risk assessments the limits of scientific knowledge, the remaining uncertainties, and the desire to identify errors of either overestimation or underestimation.
- EPA should develop guidelines for quantifying and communicating uncertainty (e.g., for models and data sets) as it occurs into each step in the risk-assessment process.
- Despite the advantages of developing consistent risk assessments between agencies by using common assumptions (e.g., replacing surface area with body weight to the 0.75 power), EPA should indicate other methods, if any, that might be more accurate.
- When ranking risks, EPA should consider the uncertainties in each estimate, rather than ranking solely on the basis of point estimate value. Risk managers should not be given only a single number or range of numbers. Rather, they should be given risk characterizations that are as robust (i.e., complete and accurate) as can be feasibly developed.

Aggregation

Typically, people at risk are exposed to a mixture of chemicals, each of which might be associated with an increased probability of one or more health effects. In such cases, data are often available on only one of the adverse effects

(e.g., cancer) associated with each chemical. At issue is how best to characterize and estimate the potential aggregate risk posed by exposure to a mixture of toxic chemicals. Furthermore, emitted substances might be carried to and deposited on other media, such as water and soil, and cause people to be exposed via routes other than inhalation, e.g., by dermal absorption or ingestion. EPA has not yet indicated whether it will consider multiple exposure routes for regulation under the 1990 Amendments, although it has done so in other regulatory contexts, e.g., under Superfund.

EPA adds the risks related to each chemical in a mixture in developing its risk estimate. This is generally considered appropriate when the only risk characterization needed is a point estimate for use in screening. When a more comprehensive uncertainty characterization is desired, EPA should adopt the following recommendations.

Recommendations

- EPA should consider using appropriate statistical (e.g., Monte Carlo) procedures to aggregate cancer risks from exposure to multiple compounds.
- In the analysis of animal bioassay data on the occurrence of multiple tumor types, the cancer potencies should be estimated for each relevant tumor type that is related to exposure, and the individual potencies should be summed for those tumors.
- Quantitative uncertainty characterizations conducted by EPA should appropriately reflect the difference between uncertainty and interindividual variability.

Communicating Risk

Certain expressions of probability are subjective, whether qualitative (e.g., that a threshold might exist) or quantitative (e.g., that there is a 90% probability that a threshold exists). Although quantitative probabilities could be useful in conveying the judgments of individual scientists to risk managers and to the public, the process of assessing probabilities is difficult. Because substantial disagreement and misunderstanding concerning the reliability of single numbers or even a range of numbers can occur, the basis for the numbers should be set forth clearly and in detail.

Recommendation

- Risk managers should be given characterizations of risk that are both qualitative and quantitative, i.e., both descriptive and mathematical.

An Iterative Approach

Resources and data are not sufficient to perform a full-scale risk assessment on each of the 189 chemicals listed as hazardous air pollutants in the 1990 Amendments, and in many cases no such assessment is needed. After MACT is applied, it is likely that some of the chemicals will pose only de minimis risk (a risk of adverse health effects of one in a million or less). For these reasons, the committee believes that EPA should undertake an iterative approach to risk assessment. An iterative approach would start with relatively inexpensive screening techniques—such as a simple, conservative transport model—and then for chemicals suspected of exceeding de minimis risk move on to more resource-intensive levels of data-gathering, model construction, and model application. To guard against serious underestimations of risk, screening techniques must err on the side of caution when there is uncertainty about model assumptions or parameter values.

Recommendations

- EPA should develop the ability to conduct iterative risk assessments that would allow improvements to be made in the estimates until (1) the risk is below the applicable decision-making level, (2) further improvements in the scientific knowledge would not significantly change the risk estimate, or (3) EPA, the emission source, or the public determines that the stakes are not high enough to warrant further analysis. Iterative risk assessments would also identify needs for further research and thus provide incentives for regulated parties to undertake research without the need for costly, case-by-case evaluations of each individual chemical. Iteration can improve the scientific basis of risk-assessment decisions while responding to risk-management concerns about such matters as the level of protection and resource constraints.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

The committee's findings are dominated by four central themes:

- Because of limitations on time, resources, scientific knowledge, and available data, EPA should generally retain its conservative, default-based approach to risk assessment for screening analysis in standard-setting; however, several corrective actions are needed to make this approach more effective.
- EPA should develop and use an iterative approach to risk assessment. This will lead to an improved understanding of the relationship between risk assessment and risk management and an appropriate blending of the two.
- The iterative approach proposed by the committee allows for improvements in the default-based approach by improving both models and the data used in analysis. For this approach to work properly, however, EPA needs to provide

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- When EPA reports estimates of risk to decision-makers and the public, it should present not only point estimates of risk, but also the sources and magnitudes of uncertainty associated with these estimates.

Risk assessment is a set of tools, not an end in itself. The limited resources available should be spent to generate information that helps risk managers to choose the best possible course of action among the available options.

SCIENCE and JUDGMENT in Risk Assessment

The public depends on realistic, accurate risk assessment from the federal government and the scientific community to learn the facts about pollution. When risk estimates turn out to be overblown—or when risks are overlooked—public skepticism abounds. This comprehensive and readable book explores how the U.S. Environmental Protection Agency (EPA) can improve its risk assessment practices under the 1990 Clean Air Act Amendments and other regulatory statutes. With a wealth of detailed information, pertinent examples, and revealing analysis, the volume explores the assumptions made by risk analysts, how to deal with uncertainty, and other basic concepts. It offers two views of EPA operations: The first examines how EPA currently assesses exposure to hazardous pollutants, evaluates the toxicity of a substance, and characterizes the risk to the public. The second, more holistic, view explores how EPA can improve the validity and credibility of its risk assessments by more fully utilizing scientific data and more fully divulging the limits of knowledge.

Also of interest . . .

Risk Assessment in the Federal Government
Managing the Process

Popularly called the "Red Book," this volume evaluates past efforts to develop and use risk assessment guidelines, reviews the experience of regulatory agencies with different administrative arrangements for risk assessment, and evaluates various proposals to modify procedures. The book's conclusions and recommendations can be applied across the entire field of environmental health.

ISBN 0-309-03349-7; 1983, 191 pages, 6 x 9, paperbound

Pesticides in the Diets of Infants and Children

This book explores whether infants and children differ from adults in susceptibility and in dietary exposures to pesticide residues and, if so, whether present regulatory approaches adequately protect them. The book summarizes the current status of pesticide use, relevant data collection methods such as food consumption surveys, methods for toxicity testing, and federal pesticide regulation. It details the special characteristics of children—growth, development, metabolism—and analyzes toxicity information based on their exposure to pesticides in the diet.

ISBN 0-309-04875-3; 1993, 408 pages, 6 x 9, index, paperbound

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